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<p>(54) Title: NEW USE</p> <p>(57) Abstract</p> <p>Macrolide compounds, such as the FK506 Substance and its related compounds are provided for the prevention or treatment of adult respiratory distress syndrome. Composition containing such compounds is also disclosed.</p>		

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## DESCRIPTION

## NEW USE

## TECHNICAL FIELD

This invention relates to a new use of macrolide compounds for pulmonary diseases. More specifically, this invention relates to a new use of macrolide compounds for preventing or treating adult respiratory distress syndrome (hereinafter, ARDS).

## BACKGROUND ART

The ARDS has been recognized as a part of systemic inflammatory response syndrome (SIRS) or multiple organ dysfunction syndromes (MODS). It is a life-threatening inflammatory lung condition characterized by severe acute hypoxemia, respiratory distress and pulmonary edema. In spite of the advances in ventilator and circulation therapy, it is reported that the mortality rate of patients with ARDS still remains high and it exceeds 50%.

Recently, no selective pharmacotherapy is available for ARDS. At present, in a clinical use, glucocorticoid anti-inflammatory steroids, which are very potent immunosuppressive agents, have not proved to be beneficial (TiPS, 14:436-441, 1993). Even high-dose glucocorticoid therapy of patients at risk of developing ARDS neither improved the clinical outcome nor reversed ARDS progression (Chest. 103:932-943, 1993).

## DISCLOSURE OF INVENTION

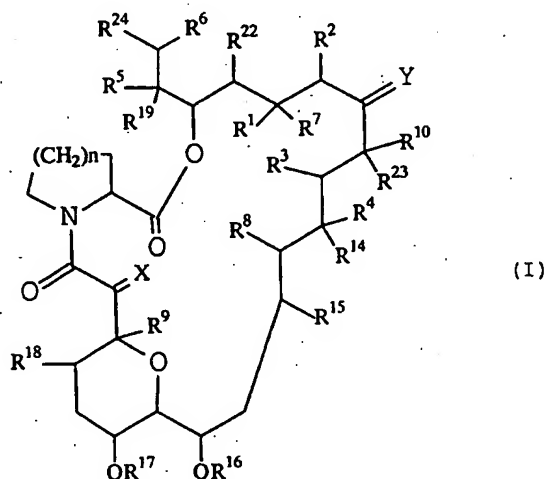
The inventors of this invention have surprisingly found that the macrolide compounds mentioned here-in-below are useful for preventing or treating ARDS.

Accordingly, this invention provides a new use of the macrolide compounds for preventing or treating ARDS.

Further, this invention provides a prophylactic or therapeutic agent for ARDS, which comprises the macrolide compounds.

Still further, this invention provides a method for preventing or treating ARDS, which comprises administering said macrolide compounds to mammals.

As a particular example of the macrolide compounds, the tricyclic compound of the following formula (I), or its pharmaceutically acceptable salt, can be exemplified.



(wherein each of adjacent pairs of  $R^1$  and  $R^2$ ,  $R^3$  and  $R^4$ , and  $R^5$  and  $R^6$  independently

(a) is two adjacent hydrogen atoms, but  $R^2$  may also be an

alkyl group or

(b) may form another bond formed between the carbon atoms to which they are attached;

R<sup>7</sup> is a hydrogen atom, a hydroxy group, a protected hydroxy group, or an alkoxy group, or an oxo group together with R<sup>1</sup>;

R<sup>8</sup> and R<sup>9</sup> are independently a hydrogen atom or a hydroxy group;

R<sup>10</sup> is a hydrogen atom, an alkyl group, an alkyl group substituted by one or more hydroxy groups, an alkenyl group, an alkenyl group substituted by one or more hydroxy groups, or an alkyl group substituted by an oxo group;

X is an oxo group, (a hydrogen atom and a hydroxy group), (a hydrogen atom and a hydrogen atom), or a group represented by the formula -CH<sub>2</sub>O-;

Y is an oxo group, (a hydrogen atom and a hydroxy group), (a hydrogen atom and a hydrogen atom), or a group represented by the formula N-NR<sup>11</sup>R<sup>12</sup> or N-OR<sup>13</sup>;

R<sup>11</sup> and R<sup>12</sup> are independently a hydrogen atom, an alkyl group, an aryl group or a tosyl group;

R<sup>13</sup>, R<sup>14</sup>, R<sup>15</sup>, R<sup>16</sup>, R<sup>17</sup>, R<sup>18</sup>, R<sup>19</sup>, R<sup>22</sup> and R<sup>23</sup> are independently a hydrogen atom or an alkyl group;

R<sup>24</sup> is an optionally substituted ring system which may contain one or more heteroatoms;

n is an integer of 1 or 2; and

in addition to the above definitions, Y, R<sup>10</sup> and R<sup>23</sup>, together with the carbon atoms to which they are attached, may represent

a saturated or unsaturated 5- or 6-membered nitrogen, sulfur and/or oxygen containing heterocyclic ring optionally substituted by one or more groups selected from the group consisting of an alkyl, a hydroxy, an alkoxy, a benzyl, a group of the formula  $-\text{CH}_2\text{Se}(\text{C}_6\text{H}_5)$ , and an alkyl substituted by one or more hydroxy groups.

Preferable  $\text{R}^{24}$  may be cyclo( $\text{C}_{5-7}$ )alkyl group, and the following ones can be exemplified.

- (a) a 3,4-di-oxo-cyclohexyl group;
- (b) a 3- $\text{R}^{20}$ -4- $\text{R}^{21}$ -cyclohexyl group,

in which  $\text{R}^{20}$  is hydroxy, an alkoxy group, an oxo group, or a  $-\text{OCH}_2\text{OCH}_2\text{CH}_2\text{OCH}_3$  group, and

$\text{R}^{21}$  is hydroxy,  $-\text{OCN}$ , an alkoxy group, a heteroaryloxy which may be substituted by suitable substituents, a  $-\text{OCH}_2\text{OCH}_2\text{CH}_2\text{OCH}_3$  group, a protected hydroxy group, chloro, bromo, iodo, aminooxalyloxy, an azido group, p-tolyloxythiocarbonyloxy, or  $\text{R}^{25}\text{R}^{26}\text{CHCOO}-$ ,

in which  $\text{R}^{25}$  is optionally protected hydroxy or protected amino, and

$\text{R}^{26}$  is hydrogen or methyl, or

$\text{R}^{20}$  and  $\text{R}^{21}$  together form an oxygen atom in an epoxide ring; or

- (c) cyclopentyl group substituted by methoxymethyl, optionally

protected hydroxymethyl, acyloxymethyl

(in which the acyl moiety optionally contains either a dimethylamino group which may be quaternized, or a carboxy group which may be esterified), one or more amino and/or hydroxy groups which may be protected, or aminooxalyloxymethyl. A preferred example is a 2-formyl-cyclopentyl group.

The definitions used in the above general formula (I) and the specific and preferred examples thereof are now explained and set forth in detail.

The term "lower" means, unless otherwise indicated, a group having 1 to 6 carbon atoms.

Preferable examples of the "alkyl groups" and an alkyl moiety of the "alkoxy group" include a straight or branched chain aliphatic hydrocarbon residue, for example, a lower alkyl group such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl, neopentyl and hexyl.

Preferable examples of the "alkenyl groups" include a straight or branched chain aliphatic hydrocarbon residue having one double-bond, for example, a lower alkenyl group such as vinyl, propenyl (e.g., allyl group), butenyl, methylpropenyl, pentenyl and hexenyl.

Preferable examples of the "aryl groups" include phenyl, tolyl, xylyl, cumenyl, mesityl and naphthyl.

Preferable protective groups in the "protected hydroxy

groups" and the "protected amino" are 1-(lower alkylthio)-(lower)alkyl group such as a lower alkylthiomethyl group (e.g., methylthiomethyl, ethylthiomethyl, propylthiomethyl, isopropylthiomethyl, butylthiomethyl, isobutylthiomethyl, hexylthiomethyl, etc.), more preferably  $C_1-C_4$  alkylthiomethyl group, most preferably methylthiomethyl group;

trisubstituted silyl group such as a tri(lower)alkylsilyl (e.g., trimethylsilyl, triethylsilyl, tributylsilyl, tert-butyldimethylsilyl, tri-tert-butylsilyl, etc.) or lower alkyl-diarylsilyl (e.g., methyldiphenylsilyl, ethyldiphenylsilyl, propyldiphenylsilyl, tert-butyldiphenylsilyl, etc.), more preferably tri( $C_1-C_4$ )alkylsilyl group and  $C_1-C_4$  alkyldiphenylsilyl group, most preferably tert-butyldimethylsilyl group and tert-butyldiphenylsilyl group; and an acyl group such as an aliphatic, aromatic acyl group or an aliphatic acyl group substituted by an aromatic group, which are derived from a carboxylic acid, sulfonic acid or carbamic acid.

Examples of the aliphatic acyl groups include a lower alkanoyl group optionally having one or more suitable substituents such as carboxy, e.g., formyl, acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, pivaloyl, hexanoyl, carboxyacetyl, carboxypropionyl, carboxybutyryl, carboxyhexanoyl, etc.;

a cyclo(lower)alkoxy(lower)alkanoyl group optionally having one or more suitable substituents such as lower alkyl, e.g.,



cyclopropyloxyacetyl, cyclobutyloxypropionyl, cycloheptyloxybutyryl, menthyloxyacetyl, menthyloxypropionyl, menthyloxybutyryl, menthyloxypentanoyl, menthyloxyhexanoyl, etc.; a camphorsulfonyl group; or a lower alkylcarbamoyl group having one or more suitable substituents such as carboxy or protected carboxy, for example, carboxy(lower)alkylcarbamoyl group (e.g., carboxymethylcarbamoyl, carboxyethylcarbamoyl, carboxypropylcarbamoyl, carboxybutylcarbamoyl, carboxypentylcarbamoyl, carboxyhexylcarbamoyl, etc.), tri-(lower)alkylsilyl(lower)alkoxycarbonyl(lower)alkylcarbamoyl group (e.g., trimethylsilylmethoxycarbonylethylcarbamoyl, trimethylsilylethoxycarbonylpropylcarbamoyl, triethylsilylethoxycarbonylpropylcarbamoyl, tert-butyl dimethylsilylethoxycarbonylpropylcarbamoyl, trimethylsilylpropoxycarbonylbutylcarbamoyl, etc.) and so on.

Examples of the aromatic acyl groups include an aroyl group optionally having one or more suitable substituents such as nitro, e.g., benzoyl, toluoyl, xyloyl, naphthoyl, nitrobenzoyl, dinitrobenzoyl, nitronaphthoyl, etc.; and an arenesulfonyl group optionally having one or more suitable substituents such as halogen, e.g., benzenesulfonyl, toluenesulfonyl, xylenesulfonyl, naphthalenesulfonyl, fluorobenzenesulfonyl, chlorobenzenesulfonyl, bromobenzenesulfonyl, iodobenzenesulfonyl, etc.

Examples of the aliphatic acyl groups substituted by an aromatic group include ar(lower)alkanoyl group optionally

having one or more suitable substituents such as lower alkoxy or trihalo(lower)alkyl, e.g., phenylacetyl, phenylpropionyl, phenylbutyryl, 2-trifluoromethyl-2-methoxy-2-phenylacetyl, 2-ethyl-2-trifluoromethyl-2-phenylacetyl, 2-trifluoromethyl-2-propoxy-2-phenylacetyl, etc.

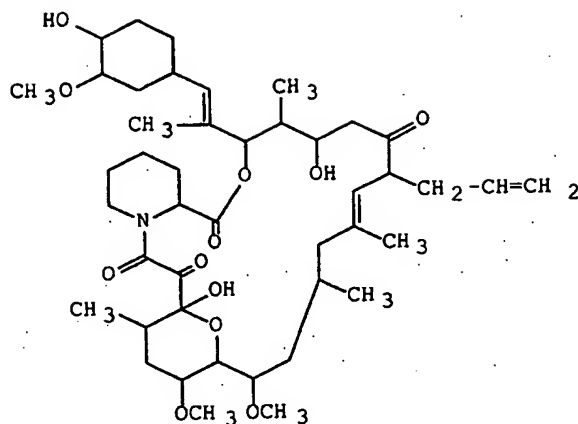
More preferable acyl groups among the aforesaid acyl groups are  $C_1$ - $C_4$  alkanoyl group optionally having carboxy, cyclo( $C_5$ - $C_6$ )alkoxy( $C_1$ - $C_4$ )alkanoyl group having two ( $C_1$ - $C_4$ ) alkyls at the cycloalkyl moiety, camphorsulfonyl group, carboxy-( $C_1$ - $C_4$ )alkylcarbamoyl group, tri( $C_1$ - $C_4$ )alkylsilyl( $C_1$ - $C_4$ )-alkoxycarbonyl( $C_1$ - $C_4$ )alkylcarbamoyl group, benzoyl group optionally having one or two nitro groups, benzenesulfonyl group having halogen, or phenyl( $C_1$ - $C_4$ )alkanoyl group having  $C_1$ - $C_4$ alkoxy and trihalo( $C_1$ - $C_4$ )alkyl group. Among these, the most preferable ones are acetyl, carboxypropionyl, menthyloxyacetyl, camphorsulfonyl, benzoyl, nitrobenzoyl, dinitrobenzoyl, iodobenzenesulfonyl and 2-trifluoromethyl-2-methoxy-2-phenylacetyl.

Preferable examples of the "5- or 6-membered nitrogen, sulfur and/or oxygen containing heterocyclic ring" include a pyrrolyl group and a tetrahydrofuryl group.

The ticyclic compounds (I) and its pharmaceutically acceptable salt for use in accordance with this invention are well known to have excellent immunosuppressive activity, antimicrobial activity and other pharmacological activities and,

as such, be of value for the treatment or prevention of rejection reactions by transplantation of organs or tissues, graft-vs.-host diseases, autoimmune diseases, and infectious diseases [EP-A-0184162, EP-A-0323042, EP-A-423714, EP-A-427680, EP-A-465426, EP-A-480623, EP-A-532088, EP-A-532089, EP-A-569337, EP-A-626385, WO89/05303, WO93/05058, WO96/31514, WO91/13889, WO91/19495, WO93/5059, etc.] , the disclosures of which are incorporated herein by reference.

Particularly, the compounds which are designated as FR900506 (=FK506), FR900520 (ascomycin), FR900523, and FR900525 are products produced by microorganisms of the genus Streptomyces, such as Streptomyces tsukubaensis No. 9993 [deposited with National Institute of Bioscience and Human Technology Agency of Industrial Science and Technology (formerly Fermentation Research Institute Agency of Industrial Science and Technology ), at 1-3, Higashi 1-chome, Tsukuba-shi, Ibaraki, Japan, date of deposit October 5, 1984, accession number FERM BP-927] or Streptomyces hygroscopicus subsp. yakushimaensis No. 7238 [deposited with National Institute of Bioscience and Human Technology Agency of Industrial Science and Technology (formerly Fermentation Research Institute Agency of Industrial Science and Technology ), at 1-3, Higashi 1-chome, Tsukuba-shi, Ibaraki, Japan, date of deposit January 12, 1985, accession number FERM BP-928][EP-A-0184162]. The FK506 Substance (general name: tacrolimus) of the following chemical formula, in particular, is a representative compound.



Chemical name: 17-allyl-1,14-dihydroxy-12-[2-(4-hydroxy-3-methoxycyclohexyl)-1-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxo-4-azatricyclo[22.3.1.0<sup>4,9</sup>]octacos-18-ene-2,3,10,16-tetraone

The preferred examples of the tricyclic compounds (I) are the ones, wherein each of adjacent pairs of R<sup>3</sup> and R<sup>4</sup> or R<sup>5</sup> and R<sup>6</sup> independently form another bond formed between the carbon atoms to which they are attached;  
 each of R<sup>8</sup> and R<sup>23</sup> is independently a hydrogen atom;  
 R<sup>9</sup> is a hydroxy group;  
 R<sup>10</sup> is a methyl group, an ethyl group, a propyl group or an allyl group;  
 X is (a hydrogen atom and a hydrogen atom) or an oxo group;  
 Y is an oxo group;  
 each of R<sup>14</sup>, R<sup>15</sup>, R<sup>16</sup>, R<sup>17</sup>, R<sup>18</sup>, R<sup>19</sup>, and R<sup>22</sup> is a methyl group;

$R^{24}$  is a 3- $R^{20}$ -4- $R^{21}$ -cyclohexyl group,

in which  $R^{20}$  is hydroxy, an alkoxy group, an oxo group, or

a  $-OCH_2OCH_2CH_2OCH_3$  group, and

$R^{21}$  is hydroxy,  $-OCN$ , an alkoxy group, a

heteroaryloxy which may be substituted by

suitable substituents, a  $-OCH_2OCH_2CH_2OCH_3$  group,

a protected hydroxy group, chloro, bromo, iodo,

aminooxalyloxy, an azido group, p-

tolyloxythiocarbonyloxy, or  $R^{25}R^{26}CHCOO-$ ,

in which  $R^{25}$  is optionally protected hydroxy

or protected amino, and

$R^{26}$  is hydrogen or methyl, or

$R^{20}$  and  $R^{21}$  together form an oxygen atom in an

epoxide ring; and

$n$  is an integer of 1 or 2.

The most preferable tricyclic compounds (I) is, in addition to FK506, ascomycin derivatives such as halogenated-ascomycin (e.g., 33-epi-chloro-33-desoxyascomycin), which is disclosed in EP 427,680, example 66a.

As the other preferable example of the macrolide compounds, rapamycin [THE MERCK INDEX (12th edition), No. 8288] and its derivatives can be exemplified. Preferred example of the derivatives is an O-substituted derivative in which the hydroxy in position 40 of formula A illustrated at page 1 of WO 95/16691,

incorporated herein by reference, is replaced by -OR<sub>1</sub> in which R<sub>1</sub> is hydroxyalkyl, hydroalkoxyalkyl, acylaminoalkyl and aminoalkyl; for example 40-O-(2-hydroxy)ethyl-rapamycin, 40-O-(3-hydroxy)propyl-rapamycin, 40-O-[2-(2-hydroxy)ethoxy]ethyl-rapamycin and 40-O-(2-acetaminoethyl)-rapamycin. These O-substituted derivatives may be produced by reacting rapamycin (or dihydro or deoxo-rapamycin) with an organic radical attached to a leaving group (for example RX where R is the organic radical which is desired as the O-substituent, such as an alkyl, allyl, or benzyl moiety, and X is a leaving group such as CCl<sub>3</sub>C(NH)O or CF<sub>3</sub>SO<sub>3</sub>) under suitable reaction conditions. The conditions may be acidic or neutral conditions, for example in the presence of an acid like trifluoromethanesulfonic acid, camphorsulfonic acid, p-toluenesulfonic acid or their respective pyridinium or substituted pyridinium salts when X is CCl<sub>3</sub>C(NH)O or in the presence of a base like pyridine, a substituted pyridine, diisopropylethylamine or pentamethylpiperidine when X is CF<sub>3</sub>SO<sub>3</sub>. The most preferable one is 40-O-(2-hydroxy)ethyl rapamycin, which is disclosed in WO94/09010, the disclosure of which is incorporated herein by reference.

The tricyclic compounds(I), and rapamycin and its derivatives, have a similar basic structure, i.e., tricyclic macrolide structure, and at least one of the similar biological properties (for example, immunosuppressive activity).

The tricyclic compounds(I), and rapamycin and its derivatives, may be in a form of its salt, which includes conventional non-toxic and pharmaceutically acceptable salt such as the salt with inorganic or organic bases, specifically, an alkali metal salt such as sodium salt and potassium salt, an alkali earth metal salt such as calcium salt and magnesium salt, an ammonium salt and an amine salt such as triethylamine salt and N-benzyl-N-methylamine salt.

With respect to the macrolide compounds usable in the present invention, it is to be understood that there may be conformers and one or more stereoisomers such as optical and geometrical isomers due to asymmetric carbon atom(s) or double bond(s), and such conformers and isomers are also included within the scope of the present invention. And further, the macrolide compounds can be in the form of a solvate, which is included within the scope of the present invention. The solvate preferably include a hydrate and an ethanolate.

The macrolide compounds usable in the present invention may be administered as pure compounds or mixtures of compounds or preferably, in a pharmaceutical vehicle or carrier.

The pharmaceutical compositions of this invention can be used in the form of a pharmaceutical preparation, for example, in solid, semisolid or liquid form, which contains the macrolide

compounds of the present invention, as an active ingredient, in admixture with an organic or inorganic carrier or excipient suitable for external(topical), enteral, intravenous, intramuscular, or parenteral applications. The active ingredient may be compounded, for example, with the usual non-toxic, pharmaceutically acceptable, carriers for tablets, pellets, capsules, eye drops, suppositories, solutions (saline, for example), emulsion, suspensions (olive oil, for example), ointment and any other form suitable for use. The carriers which can be used are water, glucose, lactose, gum acacia, gelatin, mannitol, starch paste, magnesium trisilicate, talc, corn starch, keratin, colloidal silica, potato starch, urea and other carriers suitable for use in manufacturing preparations, in solid, semisolid, or liquid form, and in addition auxiliary, stabilizing, thickening and coloring agents and perfumes may be used. The active object compound is included in the pharmaceutical composition in an effective amount sufficient to produce the desired effect upon the process or condition of the disease.

Mammals which may be treated using the method of the present invention include livestock mammals such as cows, horses, etc., domestic animals such as dogs, cats, rats, etc. and humans.

While the dosage of therapeutically effective amount of the macrolide compounds varies from and also depends upon the age and condition of each individual patient to be treated, a daily dose of about 0.0001-1000 mg, preferably 0.001-500 mg and



more preferably 0.01-100 mg of the active ingredient is generally given for treating diseases, and an average single dose of about 0.001-0.01mg, 0.2-0.5 mg, 1 mg, 5 mg, 10 mg, 50 mg, 100 mg, 250 mg and 500 mg is generally administered. Daily doses for chronic administration in humans will be in the range of about 0.1-0.3 mg/kg/day. Most preferably, the macrolide compounds can be administered to humans by intravenously in proper forms for such administration.

The following examples illustrate the present invention in further detail, it being to be understood that those examples are not intended to limit the scope of the invention.

#### Example 1

FK 506 Substance	1 g
Hydroxypropyl methylcellulose 2910 (TC-5R)	1 g
Lactose	2 g
Croscarmellose sodium (Ac-Di-Sol)	1 g

The FK 506 Substance (1 g) was dissolved in ethanol (10 ml), and thereto was added hydroxypropyl methylcellulose 2910 (TC-5R) (1 g) to prepare a suspension. To this suspension was added dichloromethane (5 ml) to prepare a homogeneous solution. Lactose (2 g) and croscarmellose sodium (Trade Mark: Ac-Di-Sol, maker: Asahi Chemical Industry) were homogeneously suspended to this solution, and then the organic solvent was

removed by evaporation. The residual product was dried under reduced pressure for 10 hours by vacuum dryer, milled for 2 minutes by coffee mill and then passed through a sieve (32 mesh) to give the solid dispersion composition of FK 506 Substance (5 g). This composition was capsulated by a conventional manner to provide capsules containing 1 mg or 5 mg of FK 506 Substance per each capsule.

#### Example 2

FK506 Substance	10mg
HCO-60	400mg
(polyoxyethylenehydrogenated castor oil 60)	
Ethanol	to 1 ml

The solution comprising the ingredients stated above is prepared by dissolving the FK506 Substance and HCO-60 in ethanol by a conventional manner. It can be administered via intravenous infusion by diluting with a proper volume of physiological saline.

#### Example 3

The efficacy of FK506 Substance on ARDS-model was evaluated in accordance with the below-mentioned method.

##### Methods:

Fifteen dogs weighing 10.0-15.0 kg were anesthetized with 50 mg/kg of intravenous sodium pentobarbital. After the anesthesia, trachea was exposed and incised, followed by

cannulation for artificial ventilation with a mixture of 30 %  $O_2$  and 70 %  $N_2$  (tidal volume:180 ml/breath; respiration rate:15-20 breaths/min) and the measurement of airway pressure.

Instrumentation included insertions of both bilateral central venous and aortic polyethylene catheters, and introduction of 7F SwanGanz catheter into main pulmonary line. Mean arterial pressure, heart rate, central venous pressure, pulmonary pressure were monitored and recorded continuously. Cardiac output was measured in duplicate using the thermodilution technique. Samples obtained from aortic line, related to various pulmonary functions, such as arterial blood  $O_2$  tension ( $PaO_2$ ), hemoglobin oxygen saturation ( $SO_2$ ) and shunt % etc, were analyzed. After the surgical preparation has been completed, the animal was left to stabilize (to ensure arterial carbon dioxide tension:  $PaCO_2$ ; ranging from 35-45 mmHg and pH; from 7.35-7.45) before the start of the study. Heating pads were used to prevent hypothermia. At the end of consecutive experiment, the animals were killed with hemorrhage and left lung was used to determine both lung wet and dry ratio. All animals receiving intravenous administration of 0.5 mg/kg of Lipopolysaccharide (LPS) and 30  $\mu$ g/kg of Phorbol myristate acetate (PMA) were divided into 3 groups. In the first group of 5 animals receiving LPS and PMA (served as control), saline was infused throughout the study. In the second group of 5 animals, Methylprednisolone (MP) was given intravenously as an infusion (30 mg/kg) for 30 min soon after LPS/PMA injection. In the third group, FK506

Substance was given intravenously as an infusion (0.025 mg/kg/hr) starting 30 min prior to LPS/PMA injection and continued throughout the duration of the experiment (until 6h post-LPS/PMA injection). Measurement of each hemodynamic parameter and analysis of arterial and venous blood gas were performed in every hour after the LPS/PMA administration. Each lung sample from left lower lobe was placed in container, weighed immediately after being taken out, and then dried in an oven (Sanyo, TSE) at 105°C for 24h. Then, the dry tissue weight was measured. W/D ratio calculated to evaluate the degree of lung edema. W/D ratio was estimated as follows;

W/D ratio = net wet weight of lung/net dry weight of lung.  
All data are presented as mean  $\pm$  standard error (S.E.). ANOVA and Dunnett's multiple comparison test or Student-t test were applied to access statistical significance between groups. A value of  $p < 0.05$  were considered as significant differences between groups.

#### Results:

A difference with change in each hemodynamic parameter failed to be perceived among all 3 groups. Although in respect of each parameter related to pulmonary function there was a similar change in control and MP group, there was the marked improvement of  $\text{PaO}_2$ ,  $\text{SO}_2$  and shunt % in FK 506 Substance. Moreover, lung wet/dry ratio in FK 506 Substance tended to decrease ( $5.22 \pm 0.23$ ), in contrast to that in control ( $6.46 \pm 0.85$ ) and MP ( $7.84 \pm 0.75$ ) group. Treatment with FK506 Substance led to

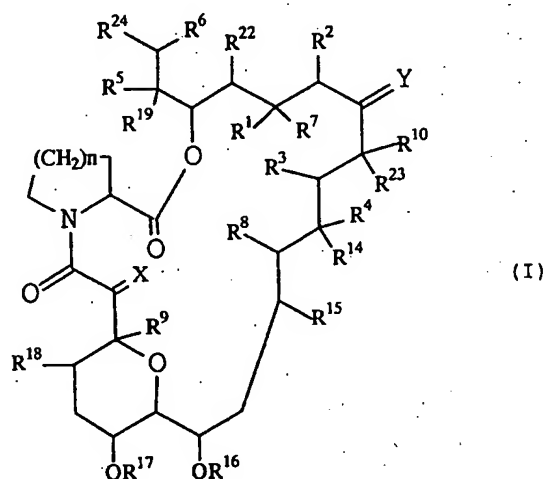
reverse the above ratio dose-dependently.

The above results indicate that the macrolides compounds such as FK506 Substance have therapeutic effect against ARDS, and/or acute lung injury.

The patents, patent applications and publications cited herein are incorporated by reference.

## CLAIMS

1. A use of macrolide compounds for manufacturing a medicament for preventing or treating adult respiratory distress syndrome.
2. The use of Claim 1, in which the macrolide compounds is the tricyclic compounds of the following formula (I):



(wherein each of adjacent pairs of R<sup>1</sup> and R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup>, and R<sup>5</sup> and R<sup>6</sup> independently

(a) is two adjacent hydrogen atoms, but R<sup>2</sup> may also be an alkyl group or

(b) may form another bond formed between the carbon atoms to which they are attached;

R<sup>7</sup> is a hydrogen atom, a hydroxy group, a protected hydroxy group, or an alkoxy group, or an oxo group together with R<sup>1</sup>;

R<sup>8</sup> and R<sup>9</sup> are independently a hydrogen atom or a hydroxy group;

R<sup>10</sup> is a hydrogen atom, an alkyl group, an alkyl group substituted

by one or more hydroxy groups, an alkenyl group, an alkenyl group substituted by one or more hydroxy groups, or an alkyl group substituted by an oxo group;

X is an oxo group, (a hydrogen atom and a hydroxy group), (a hydrogen atom and a hydrogen atom), or a group represented by the formula  $-\text{CH}_2\text{O}-$ ;

Y is an oxo group, (a hydrogen atom and a hydroxy group), (a hydrogen atom and a hydrogen atom), or a group represented by the formula  $\text{N}-\text{NR}^{11}\text{R}^{12}$  or  $\text{N}-\text{OR}^{13}$ ;

$\text{R}^{11}$  and  $\text{R}^{12}$  are independently a hydrogen atom, an alkyl group, an aryl group or a tosyl group;

$\text{R}^{13}$ ,  $\text{R}^{14}$ ,  $\text{R}^{15}$ ,  $\text{R}^{16}$ ,  $\text{R}^{17}$ ,  $\text{R}^{18}$ ,  $\text{R}^{19}$ ,  $\text{R}^{22}$  and  $\text{R}^{23}$  are independently a hydrogen atom or an alkyl group;

$\text{R}^{24}$  is an optionally substituted ring system which may contain one or more heteroatoms;

n is an integer of 1 or 2; and

in addition to the above definitions, Y,  $\text{R}^{10}$  and  $\text{R}^{23}$ , together with the carbon atoms to which they are attached, may represent a saturated or unsaturated 5- or 6-membered nitrogen, sulfur and/or oxygen containing heterocyclic ring optionally substituted by one or more groups selected from the group consisting of an alkyl, a hydroxy, an alkoxy, a benzyl, a group of the formula  $-\text{CH}_2\text{Se}(\text{C}_6\text{H}_5)$ , and an alkyl substituted by one or more hydroxy groups; or its pharmaceutically acceptable salt.

3. A method for preventing or treating adult respiratory distress syndrome, which comprises administering macrolide

compounds to mammals.

4. A pharmaceutical composition for treating or preventing adult respiratory distress syndrome, which comprises macrolide compounds in admixture with a carrier or excipient.

5. A use of the macrolide compounds for treating or preventing adult respiratory distress syndrome.

6. The macrolide compound used in Claims 1 to 5 is FK 506 Substance.



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## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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<b>(21) International Application Number:</b> PCT/GB99/01600 <b>(22) International Filing Date:</b> 20 May 1999 (20.05.99)  <b>(30) Priority Data:</b> 9810949.9 22 May 1998 (22.05.98) GB  <b>(71) Applicant (for all designated States except US):</b> HEWLETT HEALTHCARE LIMITED [GB/GB]; 1 Mill, The Wharf, Shardlow, Derby DE72 2GH (GB).  <b>(72) Inventor; and</b> <b>(75) Inventor/Applicant (for US only):</b> HAWTIN, Brian [GB/GB]; Aston Grange, Oaker, Matlock, Matlock, Derbyshire DE4 2JJ (GB).  <b>(74) Agent:</b> BASSETT, Richard; Eric Potter Clarkson, Park View House, 58 The Ropewalk, Nottingham NG1 5DD (GB).		<b>(81) Designated States:</b> AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).  <b>Published</b> With international search report. With amended claims.
<b>(54) Title:</b> PHARMACEUTICAL COMPOSITIONS COMPRISING AN AMPHOTERIC SURFACTANT AN ALKOXYLATED CETYL ALCOHOL AND A POLAR DRUG  <b>(57) Abstract</b>  A formulation, for example an oil-in-water emulsion, comprising an amphoteric surfactant, alkoxyated cetyl alcohol and a polar drug. The drug may be sodium cromoglycate or nedocromil sodium. The formulation may be useful in the treatment of skin disease such as atopic dermatitis.		

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## PHARMACEUTICAL COMPOSITIONS COMPRISING AN AMPHOTERIC SURFACTANT AN ALKOXYLATED CETYL ALCOHOL AND A POLAR DRUG

The present invention concerns formulations for the topical administration of drugs.

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Sodium cromoglycate (termed cromolyn sodium in the USA and variously also known as disodium cromoglycate or disodium 5,5'-[(2-hydroxytrimethylene)dioxy]bis-[4-oxo-4*H*-1-benzopyran-2-carboxylate]) is known to have beneficial effects in the treatment of atopic conditions, particularly asthma. Some positive results have been obtained in clinical trials addressing its efficacy with regard to atopic dermatitis (also known as eczema or atopic eczema) and associated skin disorders.

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Atopic dermatitis is an inflammatory skin disorder, affecting up to 10% of the paediatric population. It is characterised by extreme itching, a chronic relapsing course and specific distribution around the body. There is usually a family history of allergy and the condition starts in early infancy.

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Typical treatment regimes are to use simple emollients or topical corticosteroids. Long-term use of topical corticosteroids may have undesirable side effects, particularly in children.

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Topical preparations containing sodium cromoglycate have been attempted (ointments, aqueous solutions and creams) but their clinical effect has been disappointing. This may be due to low bioavailability of sodium cromoglycate in the dermis, which may arise from poor penetration of the skin. Sodium cromoglycate is likely to have poor skin penetration properties arising from its extremely polar nature.

25

In the early 1980's it was shown that the formulations used by Haider (refs 1 to 5) were unlikely to achieve good skin penetration and Fisons developed a 4% oil in water cream formulation which had better skin penetration in model experiments. This was used in a clinical trial programme of which 3 trials were published (18, 19, 20). Only one of these trials by Arianayagam *et al* (20) showed positive effects. In this study, a significant effect was seen on the total eczema score after 9 and 12 weeks of treatment. It was also shown that the greatest effect was seen in those subjects with a Total Serum IgE of <500 U/ml. However the skin penetration of this formulation was relatively poor with the calculated bioavailability of the applied dose ranging from 0.01% to 2.75%. This compares to a bioavailability of 10-15% when the drug is administered by inhalation in the treatment of asthma (21).

In 1990 Kimata and Igarishi (22) published a 4 week, placebo-controlled, double-blind trial of 1% aqueous solution of sodium cromoglycate. After application of the aqueous solution the skin was occluded with white soft paraffin. All patients had moderate to severe atopic dermatitis with Total Serum IgE levels ranging from 100 to 8600 U/ml. The sodium cromoglycate treated group exhibited significant benefits on the skin after one week's treatment and on the itch and sleep disturbance after two weeks. Further studies were published as Kimata and Hiratsuka (23) and Hiratsuka *et al* (24).

The results of topical sodium cromoglycate in atopic dermatitis are extremely variable. This may be result of the different formulations, or concentrations used or the patient population selected or a combination of all three. The concentrations used have ranged from 1% to 10% and the formulations include aqueous solution, creams and ointments. The most

positive results have been seen in relatively young children (Range 6 months to 7 years) who are strongly atopic (Serum IgE >2SD from normal).

- 5 It is also probable that adequate skin penetration of the drug is an essential pre-requisite of clinical efficacy in order for the drug to attach to the receptors responsible for the allergic inflammation and itch. Sodium cromoglycate is an extremely polar compound and may have poor penetration of skin and mucous membranes. Little is known about its  
10 absorption through the skin in patients apart from the formulation used by Ariyanayagam *et al* which gave relatively low levels of absorption. Hiratsuka *et al* were unable to detect any sodium cromoglycate in the blood using a radioimmunoassay after applying an aqueous solution of the drug but it would seem unlikely that the drug was not absorbed in view of  
15 the demonstrated effects on B cell activity and on cytokine release. Sodium cromoglycate is not metabolised and is rapidly removed from the blood and the levels may have been below the level of detection. Urinary levels over time are probably a better measure of bioavailability. Haider encouraged his patients to rub the ointment into the skin (personal  
20 communication) which may have increased the penetration.

At the publication of the first Japanese trial the journal carried an editorial (28) which stated "*Given the frequent adverse effects of therapeutic alternatives, it certainly seems worth pursuing the potential benefits of*  
25 *topical cromolyn solution. ... An effective, safe new drug to be used in the treatment of this troublesome disease would be very welcome.*"

There is therefore a long-felt interest in and need for the development of an acceptable vehicle that allows adequate skin penetration of sodium

cromoglycate, for use in the treatment of atopic dermatitis. So far a suitable vehicle has not been found, despite much interest in the area. Such a vehicle may be useful in a product that may fit as a maintenance treatment, particularly in children, between simple emollients and topical corticosteroids which at present are the mainstay treatment for this condition (27).

Ariyanayagam *et al* (20), for example, report that Bodor *et al* (1980; *Int J Pharmaceut* 7, 63) have produced a series of lipophilic pro-drugs in an attempt to improve the bioavailability of sodium cromoglycate.

As discussed above, oil-in-water emulsions comprising sodium cromoglycate (or the related chromone nedocromil sodium) are known. Some of these emulsions further comprise anionic surfactants. None comprise amphoteric surfactants, nor is the use of amphoteric surfactants suggested. None comprise alkoxylated cetyl alcohol, a substance used as a water soluble surface active emollient in personal care products.

GB 2 202 145 B, for example, describes several topical formulations of nedocromil sodium (sodium 9-ethyl-6,9-dihydro-4,6-dioxo-10-propyl-4H-pyrano(3,2-g)quinoline-2,8-dicarboxylate), including an oil-in-water emulsion.

Ishikura *et al* (1987) *Drug Design & Delivery* 1, 285-295 describes the use of amphoteric surfactants in improving percutaneous uptake of diltiazem hydrochloride (used as an example of a cationic water soluble drug) from water-soluble films. Whilst investigation of uptake of sodium cromoglycate (used as an example of an anionic water soluble drug) was

also reported in the paper, the effect of the amphoteric surfactants on sodium cromoglycate uptake was not suggested or tested.

The present work surprisingly shows that a composition, for example an oil-in-water emulsion, comprising an amphoteric surfactant, alkoxylated cetyl alcohol and a polar drug, for example sodium cromoglycate, may be formed. The composition has been found to be stable, and an effective amount of the drug may penetrate the skin of a patient when the formulation is applied topically. The composition may be useful in the treatment of skin disease such as atopic dermatitis.

The composition of the present invention avoids anionic or cationic substances and provides a stable formulation, for example a stable emulsion, comprising the polar substance sodium cromoglycate. The polarity of sodium cromoglycate may limit the stability of known emulsions. The amphoteric surfactant may assist in overcoming this problem and may also assist the skin penetration of the sodium cromoglycate. Use of alkoxylated cetyl alcohol and an amphoteric surfactant in combination may be particularly beneficial in producing a stable and effective formulation, for example an emulsion, comprising a polar drug, for example sodium cromoglycate or nedocromil sodium.

Thus, a first aspect of the invention is a composition comprising an amphoteric surfactant, an alkoxylated cetyl alcohol and a polar drug.

25

The composition may comprise an aqueous phase and an oil phase. It may be an emulsion or may be used in the manufacture of an emulsion. It may, for example, form or be comprised in the aqueous phase of an

emulsion. It is preferred that the emulsion is an oil-in-water emulsion but it will be appreciated that the emulsion may alternatively be a water-in-oil emulsion.

5 A "polar drug" is a compound which may be used as an active ingredient in a medicament that is water-soluble and ionises on solution in distilled water at 25 °C. A "water-soluble" compound may be dissolved in distilled water at 25 °C at a ratio of compound to water (weight to volume, or volume to volume if the compound is a liquid) of at least 1 to 10000, 1  
10 to 1000, 1 to 100, 1 to 30, 1 to 10, 1 to 1 or 1 to less than 1. It is preferred that the polar drug comprises an anionic polar drug, for example a chromone, such as nedocromil sodium or sodium cromoglycate. Most preferably, the drug comprises sodium cromoglycate.

15 Other examples of polar drugs that may be suitable include polar anti-inflammatory or antirheumatic agents, for example ibuprofen; antibacterial agents, for example agents that may be useful in the treatment of acne (for example clindomycin sodium phosphate or tetracycline); a hormone, for example an oestrogen; a polar analgesic, for example fentanyl; a polar  
20 motion-sickness treatment molecule, for example scopolamine or hyoscine; an antihypertensive, for example clonidine; a vasodilator or coronary vasodilator, for example nitroglycerine; or nicotine.

Further preferred examples of suitable polar drugs include a polar  
25 corticosteroid formulation, for example a salt of an esterified corticosteroid, for example a salt of a phosphate or succinate ester. Such polar formulations may be soluble in water and are the form commonly used for injections or solutions. Suitable salts of esters of corticosteroids include betamethasone sodium phosphate, dexamethasone sodium



phosphate, hydrocortisone sodium phosphate, hydrocortisone sodium succinate, methylprednisolone sodium succinate and prednisolone sodium succinate.

- 5 The drug may be useful in treating skin disease or may be a drug that is useful when administered transdermally.

The drug, for example sodium cromoglycate, may constitute from 0.01 to 20% w/v, preferably 0.1 to 20% w/v, still more preferably 1 to 10% w/v, yet more preferably about 7.5% w/v, most preferably about 4% w/v of the composition, for example the emulsion. When the polar drug comprises a corticosteroid, the corticosteroid may preferably constitute 0.01 to 10% w/v, preferably from 0.1 to 10% w/v, most preferably about 0.25 or 0.5% w/v of the composition, for example the emulsion.

15

It will be appreciated that it is preferred that the above proportions are present in a composition of the invention that is a formulation, for example an emulsion, as may be administered to a patient, for example applied to the skin of the patient. It will further be appreciated that a composition of the invention may be useful in preparing a formulation, for example an emulsion, suitable for administration to a patient, for example application to the skin of a patient; for example, the composition may form the aqueous phase of the emulsion, or it may be a concentrate used in the preparation of the aqueous phase of the emulsion, as known to those skilled in the art. Thus, it will be appreciated that in these examples of compositions of the invention, it may be preferred that the proportion of the composition that is the polar drug may be from about 1.5 to about 10 times greater than that given above.

25

It will be appreciated that the composition, for example emulsion, may comprise more than one polar drug. Thus, for example, a preferred composition, for example emulsion, of the invention may comprise a chromone, such as nedocromil sodium or sodium cromoglycate, and a corticosteroid. The corticosteroid may constitute 0.01 to 10% w/v, preferably from 0.1 to 10% w/v, most preferably about 0.25 or 0.5% w/v of the emulsion or other formulation as administered to a patient, as above. Preferences for the corticosteroid are as given above; most preferably it is betamethasone sodium phosphate.

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It is preferred that an emulsion is stable. By this is meant that separation of the oil and water phases is not detectable by visual inspection after a period of at least one day, preferably one week, still more preferably one month, yet more preferably six months or a year after manufacture when stored at 15 °C to 30 °C. Storage may be at, for example, 22 °C.

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It will be appreciated that the composition, for example emulsion, may be presented as a lotion or as a foam, as known to those skilled in the art.

20 The term "amphoteric surfactant" is well known to those skilled in the art. Such surfactants (which may also be known as ampholytic surfactants) possess at least one anionic group and at least one cationic group, and can therefore have anionic, non-ionic or cationic properties depending on the pH. If the isoelectric point of the molecule occurs at pH7, the molecule is said to be balanced. Amphoteric surfactants may have detergent and disinfectant properties. Balanced amphoteric surfactants may be particularly non-irritant to the eyes and skin.

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Amphoteric surfactants are characterised by their ability to move between having a cationic or anionic charge dependent upon pH. In the presence of highly polar molecules such as sodium cromoglycate in a weak acid solution (for example, pH6), these surfactants may be compatible with the changes to charges around the molecule as it disassociates or associates (in the case of sodium cromoglycate, between the positive sodium and negative cromoglycate elements), providing a consistent medium for surface wetting and skin penetration.

It will be appreciated that the composition, for example emulsion, should not contain ingredients that may cause irritation to the skin, even on prolonged use. Compounds to which sensitisation may occur should be avoided. Thus, balanced amphoteric surfactants may be preferred.

The pH of skin is about 4.5. In order to avoid irritation to the skin, a pH that is slightly acidic, ie to the acid side of neutral, is preferred, for example a pH between about 4.5 and about 7.0. For example, the emulsion may be manufactured to a pH of 6.0, for example using sodium dihydrogen orthophosphate as the buffer agent.

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Examples of amphoteric surfactants include aminocarboxylic acids, aminopropionic acid derivatives, imidazoline derivatives, dodecin, pendecamine or long-chain betaines, Nikkol AM101® (2-alkyl-N-carboxymethyl-N-hydroxyethyl imidazolinium betaine), Nikkol AM310® (lauryldimethylaminoacetic acid betaine), Nissan Anon #300 (12 w/v% alkyldiaminoethylglycine hydrochloride, 3 w/v% alkyldiethylene-triaminoglycole hydrochloride; Inui Shouji Co, ADG), C31G (a mixture of alkyl betaines and alkyl amine oxides), N-tetradecyl-N,N-dimethyl-3-ammonio-1-propanesulfonate) or cocamidopropyl betaine. Any of these

may be used, but cocamidopropyl betaine may not be preferred as instances of allergy to this compound, when used in shampoo, have been reported (De Groot *et al* (1995) *Contact Dermatitis* 33(6), 419-422).

- 5 It will be appreciated that an amphoteric surfactant may be supplied (as an "amphoteric surfactant" or amphoteric surfactant preparation) packaged or compounded with other substances by the manufacturer, and that references to an amphoteric surfactant encompass an amphoteric surfactant alone and a preparation supplied as an amphoteric surfactant by the
- 10 manufacturer. It is preferred that the amphoteric surfactant is a carboxylated imidazoline derivative. It is particularly preferred that the amphoteric surfactant comprises disodium coacoamphodiacetate. It is still more preferred that the disodium coacoamphodiacetate is packaged or compounded with lauryl sulphate and hexylene glycol, as is known to
- 15 those skilled in the art.

It is particularly preferred that the amphoteric surfactant preparation has the following composition:

20	disodium coacoamphodiacetate	5 to 30% w/w, for example 14%w/w
	sodium lauryl sulphate	2 to 20% w/w, for example 12.5%w/w
	hexylene glycol	3 to 20% w/w, for example 7%w/w
	sodium chloride	0.25 to 15% w/w, for example 3.9%w/w
	lauryl alcohol	0.1 to 5% w/w, for example 1.0%w/w
25	hydrochloric acid	0.1 to 5% w/w, for example 1.0%w/w
	sodium sulphate	0.025 to 2.5% w/w, for example 0.25%w/w
	formadehyde	0.003 to 1% w/w, for example 0.03%w/w
	water	to 100%w/w

Such a preparation may be Miracare 2MCA/E™, supplied by Rhône-Poulenc Chemicals, Poleacre Lane, Woodely, Stockport, Cheshire SK6 1PQ. This preparation is very well tolerated on skin. As a strong surfactant, it may rapidly "wet-out" the skin, penetrating the skin's natural oily barrier and assisting the trans-dermal passage of the sodium cromoglycate or other polar drug. The action of breaking down the oils in the skin also enhances skin hydration from the water present in the emulsion.

- 10 The amphoteric surfactant may be incorporated in the water phase of an oil-in-water emulsion that is a preferred embodiment of the invention. This may assist skin penetration by the polar drug, for example sodium cromoglycate, and may hold the emulsion stable. In the absence of an amphoteric surfactant, the emulsion may break down over a period of 24 hours into two phases, ie the oils will separate and float to the surface. The amphoteric surfactant may constitute from 0.05 to 20% weight to volume (w/v) of the emulsion, preferably 0.1% to 10% w/v, still more preferably 1 to 5% w/v, most preferably about 2% w/v of the emulsion. It will be appreciated that the above proportions may refer to an amphoteric surfactant alone or to an amphoteric surfactant preparation, as described above, for example to a preparation comprising disodium coacoamphodiacetate, laurylsulphate and hexylene glycol, such as Miracare 2MCA/E™. Preferably, the proportions refer to an amphoteric surfactant preparation. The amphoteric surfactant component may constitute from 0.007 to 2.8% w/v, 0.014 to 1.4% w/v, 0.14 to 0.7% w/v or most preferably 0.28% w/v of the emulsion.

It will be appreciated that when determining the percentage weight to volume of an ingredient of the composition, for example emulsion, or a

solute to solvent, the weight in grams of the ingredient is compared with the volume in millilitres (ml) of the prepared composition, for example emulsion.

- 5 The term alkoxylated cetyl alcohol encompasses polypropoxylated cetyl alcohol, the chemical description given for Procetyl AWS in *Gardner's Chemical Synonyms and Trade Names*, ninth edition. Alkoxylated cetyl alcohol may be obtained from Croda Chemicals Ltd, Cowick Hall, Snaith, Goole, North Humberside, DN14 9AA. It is marketed as "Procetyl
- 10 AWS". The alkoxylated cetyl alcohol may be useful for its water soluble surface active emollient properties. It may also act as an emulsifying and solubilising agent and imparts a silky feel to the skin.

- The alkoxylated cetyl alcohol may constitute from 0.1 to 20% w/v,
- 15 preferably from 0.1 to 10% w/v, still more preferably from 0.5 to 4% w/v of the emulsion and most preferably 1% w/v of the emulsion.

- It will be appreciated that it is preferred that the above proportions may be present in a composition of the invention that is a formulation (that is not
- 20 necessarily an emulsion) that may be administered to a patient, for example applied to the skin of the patient. It will further be appreciated that a composition of the invention may be useful in preparing a formulation, for example an emulsion, suitable for administration to a patient, for example application to the skin of a patient; for example, the
- 25 composition may form the aqueous phase of the emulsion, or it may be a concentrate used in the preparation of the aqueous phase of the emulsion, as known to those skilled in the art. Thus, it will be appreciated that in these examples of compositions of the invention, it may be preferred that the proportion of the composition that is the alkoxylated cetyl alcohol or

amphoteric surfactant may be from about 1.5 to about 10 times greater than those given above.

It will be appreciated that the critical ingredients of the formulation, for example the emulsion, are the amphoteric surfactant, alkoxyated cetyl alcohol and the drug component (for example, sodium cromoglycate). Further ingredients may include water and an oil phase. Suitable components of the oil phase will be known to those skilled in the art, and the following description is not limiting.

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It is preferred that the components of an emulsion are chosen such that the emulsion is acceptable to a patient using it. For example, it should not be too greasy. It is preferred that the emulsion has an appropriate viscosity for spreading smoothly over the skin with low friction over areas of broken or sensitive skin. Thus, the emulsion may not have the appearance of a solid at 22°C or at 37°C. It is preferred that the emulsion may have a viscosity of between about 10, 20, 100, 200 or preferably 400 to 20,000 centipoise or mPas at 22°C or 37°C. It is further preferred that the emulsion has a viscosity between about 1400 to 2600 centipoise, preferably between about 2000 to 2600 centipoise, when measured at a maximum shear rate of 210sec<sup>-1</sup> and between about 2300 to 3800 centipoise, preferably between about 3000 to 3800 centipoise, when measured at maximum shear rate of 125sec<sup>-1</sup>. Methods of measuring viscosity are well known to those skilled in the art and are described, for example, in Chapter 22 of *Remington's Pharmaceutical Sciences* 15th Ed, Mac Publishing. For comparison, the viscosity of olive oil is about 138 mPas at 10°C and about 36 mPas at 40°C. The emulsion may appear as a watery lotion, which may be applied via a bottle dispenser. More preferably, the emulsion may appear as a cream which at 20°C remains in

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an open container when the container is inverted, and may be dispensed using a hand pump attached to a bottle, such as may be used for dispensing liquid hand soap. Reference 18 sets out some desirable characteristics of preparations for treating atopic dermatitis.

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The emulsion may appear as a foam which may be applied *via* a pressurised dispenser. When presented as a foam, it may be desirable for the emulsion to be more dilute with regard to excipients and the same or more concentrated with regard to the polar drug than an emulsion presented as a lotion, as described above. This may reduce the viscosity of the emulsion and aid the dispensing of the foam.

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The oil phase may comprise liquid paraffins, white soft paraffin, glycerol monostearate, non-ionic emulsifying wax or a lipophilic non-ionic surfactant (for example sorbitan tristearate), benzyl alcohol and/or isopropyl myristate. These terms are well known to those skilled in the art. Isopropyl myristate is an example of an emollient. Glycerol monostearate is an example of an emulsifying agent and may also act as an emollient. Benzyl alcohol is an example of a preservative and a mild local anaesthetic. The non-ionic emulsifying wax may be Polawax NF (a blend of higher fatty alcohols and polyoxyethylene sorbitan fatty acid ester, in particular a blend of cetostearyl alcohol and sorbitan tristearate). Non-ionic emulsifying wax may be useful in the preparation of emulsions comprising polar substances. A lipophilic non-ionic surfactant, for example sorbitan tristearate, may be used as an alternative to or in addition to a non-ionic emulsifying wax. Liquid paraffins and isopropyl myristate may act as emollients and form an occlusive film on the skin as water dries away from the emulsion. This film may assist in keeping the skin hydrated from the water applied in the emulsion.

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Liquid paraffins may provide from 0.1% to 30% w/v, preferably 1% to 20% w/v, still more preferably 5% to 15% w/v and most preferably about 10% w/v of the emulsion.

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White soft paraffin may provide from 0.1% to 30% w/v, preferably 1% to 20% w/v, still more preferably 2% to 15% w/v and most preferably about 5% w/v of the emulsion.

- 10 Glycerol monostearate may provide from 0.1 to 10% w/v, preferably 0.5% to 5% w/v, still more preferably 1% to 3% w/v, most preferably 2% w/v of the emulsion.

- 15 The nonionic emulsifying wax, for example Polawax NF, or lipophilic non-ionic surfactant, for example sorbitan tristearate, may provide from 0.1 to 15% w/v, preferably 0.5 to 5% w/v, still more preferably about 2% w/v of the emulsion. It is preferred that a lipophilic non-ionic surfactant, for example sorbitan tristearate, provides from 0.5 to 5% w/v of the emulsion or that the nonionic emulsifying wax, for example Polawax NF, provides from 2 to 5% w/v. It will be appreciated that if the nonionic emulsifying wax, for example Polawax NF provides more than about 5% of the emulsion that the resulting emulsion may be too viscous to spread easily on the skin.

- 25 Isopropyl myristate may provide from 0.1 to 10% w/v, preferably 0.5 to 5% w/v, still more preferably about 2% w/v of the emulsion.

Benzyl alcohol may provide from 0.001 to 5% w/v, preferably from 0.01 to 1.0% w/v, still more preferably about 0.2% w/v of the emulsion.

The aqueous phase comprises water and the drug. It may further comprise one or more preservatives. Disodium edetate (EDTA) and Triclosan (5-chloro-2(2,4-dichlorophenoxy)phenol) are suitable compounds with preservative properties. The drug may be in solution in the aqueous phase. EDTA may also contribute to the stability of the formulation by forming complexes with any heavy metal ions. Triclosan may have a residual antibacterial effect on the skin and may assist with limiting any damage at an eczema site arising from bacterial colonisation.

The anti-infective effect of the preservative, for example Triclosan and/or benzyl alcohol may also serve to prevent potential infection from the prolonged rubbing process involved during administration.

Disodium edetate may provide from 0.001 to 5% w/v, preferably 0.01 to 1% w/v, still more preferably about 1% w/v of the emulsion.

Triclosan (5-chloro-2(2,4-dichlorophenoxy) phenol) may provide from 0.001% to 5% w/v, preferably 0.01% to 1.0% w/v, still more preferably about 0.2% w/v of the emulsion.

The emulsion may consist essentially of the components listed below, preferably in substantially the quantities listed below. It is preferred that the drug is sodium cromoglycate or nedocromil sodium, most preferably sodium cromoglycate.

sorbitan tristearate or non-ionic emulsifying wax (Polawax NF) 2.0%  
glycerol monostearate 2.0%  
light liquid paraffin 10.0%  
white soft paraffin 5.0%

- isopropyl myristate 3.0%  
drug 7.5%  
disodium edetate 0.1%  
amphoteric surfactant 2.0% (for example disodium coacampodiacetate,  
5 which may be compounded with lauryl sulphate and hexylene glycol, for  
example Miracare 2MCA/E™)  
alkoxylated cetyl alcohol 1.0%  
triclosan 0.2%  
benzyl alcohol 0.2%  
10 purified water 67.0%

- Sorbitan tristearate may be obtained under the name Crill 35™ from Croda  
Chemicals Limited, Cowick Hall, Snaith, Goole, North Humberside  
DN14 9AA. Polawax NF may also be obtained from Croda Chemicals  
15 Limited. It is preferred that Polawax NF is used in preference to sorbitan  
tristearate (Crill 35™).

- Alternatively, the drug, for example sodium cromoglycate, may be present  
at 4.0% w/v (or 2% or 8% w/v, for example) and purified water at 70.5%  
20 (or 72.5% or 66.5%, for example).

The pH of the emulsion may be adjusted to 6.0 using sodium dihydrogen  
orthophosphate.

- 25 The emulsion may appear as a cream or a watery lotion. The lotion may  
be rubbed into the affected skin for about 3 to 5 minutes. During this  
process, the lotion may first go white, then clear and then disappear into  
the skin, leaving a protective barrier that may help to stop the skin drying  
out.

An emulsion of the invention may be prepared by methods well known to those skilled in the art. For example, it may be prepared by heating the oils to about 70 °C, then adding them steadily to the water phase (also at  
5 or about 70 °C) with good stirring, and then allowing the emulsion to cool.

Once an emulsion has been formed, further water may be added with stirring if desired, for example in preparing a formulation suitable for  
10 delivery as a foam. A suitable formulation for delivery as a foam may be prepared by diluting an emulsion essentially as described above by the addition of one part water to two parts emulsion. It will be appreciated that if an emulsion is to be diluted before application to the skin that it may be preferred that the concentration of the drug, for example sodium cromoglycate, in the emulsion may be calculated such that the desired  
15 concentration, for example 4%, is achieved in the diluted formulation. It will be appreciated that it is preferred that the emulsion is formed with the composition that it is intended to apply to the skin, for example with the additional water referred to above *ab initio* so that dilution is not  
20 necessary.

A suitable formulation for delivery as a foam may consist essentially of the components listed below, preferably in substantially the quantities listed below. It is preferred that the drug is sodium cromoglycate or  
25 nedocromil sodium, most preferably sodium cromoglycate.

sorbitan tristearate or non-ionic emulsifying wax (Polawax NF) 1.3%

glycerol monostearate 1.3%

light liquid paraffin 6.6%

- white soft paraffin 3.3 %  
isopropyl myristate 2.0 %  
drug 4 %  
disodium edetate 0.66 %  
5 amphoteric surfactant 1.3 % (for example disodium coocamphodiacetate,  
which may be compounded with lauryl sulphate and hexylene glycol, for  
example Miracare 2MCA/E™)  
alkoxylated cetyl alcohol 0.66 %  
triclosan 0.13 %  
10 benzyl alcohol 0.13 %  
purified water to 100 % (about 78.6 %)

A further aspect of the invention is a stable oil-in-water emulsion comprising sodium cromoglycate, wherein when the emulsion is applied to  
15 skin an amount of sodium cromoglycate penetrates the skin that is sufficient to produce a demonstrable effect in the treatment of atopic dermatitis/eczema.

The amount of sodium cromoglycate that penetrates skin may be measured  
20 by techniques well known to those skilled in the art, some of which are mentioned above. Methods include *in vitro* measurements on skin biopsies (which may be human or animal, preferably rodent, still more preferably hairless rat skin) or *in vivo* measurements. For example, the presence of sodium cromoglycate in plasma or urine following topical  
25 application to a human or experimental animal (for example rat or rabbit) may be measured. Such measurements are described in Ishikura *et al* (1987) cited above, and Ariyanayagam *et al* (20). Sodium cromoglycate may be quantified by techniques of analytical chemistry, for example high performance liquid chromatography (HPLC).

Effectiveness of the emulsion may be measured in animal models of atopic dermatitis, or in clinical trials on humans, for example as described in Examples 3 to 6. Preferably it is measured in humans.

5

Patients having atopic dermatitis may be diagnosed by criteria known to the skilled person. For example, patients may be diagnosed by a general medical practitioner recognising the effect of atopic eczema on the surface of the skin. Several sets of criteria for diagnosis have been proposed in order to assist in achieving consistency between studies of the condition ((29) and Williams *et al* (1996) *B J Dermatol* 135, 12-17). The criteria discussed in Williams *et al* include: a history of an itchy skin plus three or more of : (i) a history of rash in the skin creases (folds of elbows, behind the knees, fronts of ankles or around the neck); (ii) a personal history of asthma or hay fever; (iii) a history of generally dry skin in the last year; (iv) onset under the age of 2; and (v) visible flexural dermatitis as defined by a photographic protocol.

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The criteria by which an effect on atopic dermatitis may be judged are set out in reference 29.

20

It may be necessary to select patients on the basis of the level of circulating IgE. Suitable IgE tests include an *in vitro* total IgE test and an *in vitro* specific IgE test, for example the UniCAP Total (or Specific) IgE tests sold by Pharmacia & Upjohn, which use the Allergen ImmunoCAPs as the allergen reagent.

25

It may be desirable or necessary for patients to be screened according to their IgE levels before treatment with sodium cromoglycate is undertaken.

More specifically, patients with total serum IgE levels below 150 iu/ml may be less likely to respond to the treatment. It is preferred that the patient is a child between the ages of 6 months and 10 years with atopic dermatitis.

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A further aspect of the invention is a method of treatment of a skin disease or condition wherein a drug is applied to the skin of an individual affected by the disease or condition in or with a formulation comprising alkoxylated cetyl alcohol and an amphoteric surfactant. The drug may be present in a formulation comprising the alkoxylated cetyl alcohol or it may be applied to skin before, after or at the same time as the said formulation, which may or may not comprise further amounts of the same or a different drug.

15 It is preferred that the drug is a polar drug, as discussed above. The formulation may aid penetration of the drug, particularly a polar drug, through the skin by altering the nature of the barrier presented by the skin, as described above. It will however be appreciated that the drug may be a non-polar drug, for example a non-polar drug useful in the treatment of a skin disease or condition, for example a non-polar form of a corticosteroid, as found, for example, in creams prepared for topical application, for example in Betnovate™, Eumovate™ or Aureocort™ cream, as described further below. It is preferred that a non-polar drug, for example a non-polar form of a corticosteroid is applied to the skin before, 25 after, or at the same time as the said formulation, preferably substantially immediately before or substantially immediately after the said formulation, most preferably, before or immediately before the said formulation. The formulation may form a film over the surface of the skin which is beneficial, for example in retaining moisture.

Preferences for the said formulation are as for the compositions of the invention but it will be appreciated that the formulation may not comprise a polar drug if a drug is applied separately to the skin.

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It is preferred that the formulation comprises sodium cromoglycate or nedocromil sodium and/or a corticosteroid, for example a polar form of a corticosteroid such as a salt of an esterified corticosteroid, as described above. The drug may alternatively be an antibacterial agent, for example  
10 an antibacterial agent that may be useful in treating acne, as described above.

A further aspect of the invention is the use of an alkoxylated cetyl alcohol and an amphoteric surfactant in the manufacture of a medicament for the  
15 treatment of a skin disease or condition. A drug, preferably a polar drug may further be used in the manufacture of the said medicament.

In the following aspects of the invention, it is preferred that the composition or emulsion of the invention comprises sodium cromoglycate  
20 or nedocromil sodium and/or a corticosteroid, for example a polar form of a corticosteroid such as a salt of an esterified corticosteroid, as described above.

A further aspect of the invention is a method of treatment of a skin disease  
25 or condition comprising applying a composition or emulsion of the invention to the skin of an individual affected by the disease or condition.



A still further aspect of the invention is the use of a composition or emulsion of the invention in the manufacture of a medicament for the treatment of a skin disease or condition.

- 5 It is preferred that the skin disease or condition is a disease of humans, but may also be one that affects other mammals, for example cats, dogs or horses. The disease or condition may be any in which skin mast cells and/or delayed (cellular) hypersensitivity reactions and/or inflammation is thought to be involved.

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- It is preferred that the disease or condition is atopic dermatitis or eczema, but it may also be contact sensitivity, psoriasis, drug sensitivity reactions, aphthous ulcers, Behçet's syndrome, pemphigus, urticaria, urticaria pigmentosa, pyoderma gangrenosum, chronic skin ulcers, ulcers  
15 associated with Crohn's disease, burns, insect stings/bites, herpetic infections, systemic sclerosis (systemic scleroderma), morphoea (circumscribed or localised scleroderma) and dermal nodular fibrosis.

- The skin disease or condition may be being, may have been or may be  
20 further treated by application of a corticosteroid. It may be beneficial to treat a patient, particularly a patient with atopic dermatitis or eczema, with a combination of a cromone and a corticosteroid. The therapeutic effects of a cromone such as sodium cromoglycate and corticosteroids may not be wholly interchangeable, as described in Altounyan & Howell (1969)  
25 "Treatment of asthma with disodium cromoglycate (FPL 670, "Intal")" *Respiration* 26(suppl), 131-140 and in Altounyan (1979) *Proceedings of Allergy* (Pitman Medical). A minimum dose of corticosteroids may be necessary below which sodium cromoglycate is without clinical effect. Further, corticosteroids alone, even in high dosage, may not achieve the

same therapeutic response as a lower dose of corticosteroid together with sodium cromoglycate. Haider (5) suggests that sodium cromoglycate may exert a corticosteroid-sparing effect in atopic eczema or that there may be a synergism between the two.

5

The cromone and corticosteroid may be presented in the same formulation or in separate formulations. The cromone and corticosteroid may be presented as separate formulations for topical application. Either or both formulations (if appropriate) may be a composition, for example an emulsion, of the invention. As described in Examples 3 and 4, a formulation comprising a corticosteroid may be applied before or after (preferably before) a formulation of the invention comprising a cromone, for example sodium cromoglycate. The corticosteroid may be in a polar or a non-polar form; preferably it is in a non-polar form if it is not presented in a composition of the invention. Suitable formulations comprising a non-polar corticosteroid include the proprietary formulations Betnovate RD (bethamethasone valerate, ready diluted), Aureocort (triamcinolone acetonide and chlortetracycline hydrochloride (an antibiotic)), and Eumovate (clobetasone butyrate). A 1% hydrocortisone preparation may also be used.

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It will be appreciated that bethamethasone valerate and triamcinolone acetonide may be considered to be potent corticosteroids, and clobetasone butyrate may be considered to be a moderately potent corticosteroid, as classified, for example, in Martindale, the Extra Pharmacopoeia, 31<sup>st</sup> Edition. Hydrocortisone may be considered to be a mild corticosteroid. It will be appreciated that the corticosteroid preparation used in combination with an emulsion of the invention comprising a cromone may be chosen depending upon the severity of the symptoms to be treated. A

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stronger (for example, moderately potent or potent) corticosteroid may be used at the start of combination therapy, which may be replaced by a weaker (for example a mild or moderately potent) corticosteroid as the symptoms are brought under control. Thus, if the symptoms are  
5 exacerbated, for example as the result of the patient contracting a cold, then a stronger corticosteroid may be used until the symptoms are diminished, whereupon a weaker corticosteroid may be used, as described in Example 3.

10 Symptoms that may be assessed include skin itching, sleep loss and skin condition, for example redness and the presence of sores or scabs.

The compositions or emulsions of the invention comprising sodium cromoglycate or nedocromil sodium, may also be useful in the treatment  
15 of sunburn or in sunscreen preparations. They may also be useful in cosmetic preparations, for example anti-ageing creams.

A further aspect of the invention is a method of treatment of a patient in need of a polar drug comprising applying a composition or emulsion of the  
20 invention comprising the said polar drug to the skin of the said patient. The polar drug may be or may comprise, for example, a polar anti-inflammatory or antirheumatic agent, for example ibuprofen; an antibacterial agent, for example an agent that may be useful in the treatment of acne (for example clindomycin sodium phosphate or  
25 tetracycline); a hormone, for example an oestrogen; a polar analgesic, for example fentanyl; a polar motion-sickness treatment molecule, for example scopolamine or hyoscine; an antihypertensive, for example clonidine; a vasodilator or coronary vasodilator, for example nitroglycerine; or nicotine.

A still further aspect is the use of a composition or emulsion of the invention in a method of treating a patient in need of the said polar drug.

- 5 The patient in need of a polar drug may be, for example, a patient with arthritis that is in need of a polar anti-inflammatory or antirheumatic agent, for example ibuprofen. Alternatively, the patient in need of a polar drug may be a patient with acne that is in need of a polar antibacterial drug, for example clindomycin sodium phosphate or tetracycline. The
- 10 patient in need of a polar drug may be a patient in need of nicotine, for example a patient who is attempting to give up cigarette smoking. Polar drugs that may be suitable for treating particular conditions when administered transdermally will be known to those skilled in the art.
- 15 The composition or emulsion may be packaged or presented in any convenient way. For example, it may be packaged in a tube, tub, bottle or pressurised aerosol, using techniques well known to those skilled in the art and as set out in reference works such as *Remington's Pharmaceutical Sciences* 15th Ed, Mac Publishing. It is preferred that it is packaged in
- 20 such a way as to minimise contact of the unused composition or emulsion with the environment, in order to minimise contamination of the composition or emulsion both before and after the container is opened. It is particularly preferred that the composition or emulsion is packaged in a pressurised aerosol container or in a plastic dispenser bottle. For
- 25 example, an emulsion comprising sodium cromoglycate at either 4% or 8% w/v may be packaged in a plastic dispenser bottle, which may contain one month's supply (between about 150 and 300 ml).

It will be appreciated that the emulsion may have the appearance of a cream or a lotion, or of a foam.

The composition or emulsion may be applied topically to affected areas or prophylactically to unaffected areas. The composition or emulsion may be applied as directed by a physician. For example, the affected area may be rubbed, for example for at least about 5 minutes, to apply the composition or emulsion, in order to encourage absorption of the drug. The composition or emulsion may be applied once or twice a day, or at greater or lesser intervals, depending upon the needs of the patient, as determined by the patient or a physician. As described above, a composition or emulsion of the invention comprising a cromone may be applied after a formulation comprising a corticosteroid.

The invention will now be described by reference to the following, non-limiting, figures and examples.

**Figure 1:** Mean symptom score following treatment with corticosteroids and an emulsion comprising sodium cromoglycate. Details of the treatment are described in Example 3.

**Example 1: preparation of an oil-in-water emulsion comprising sodium cromoglycate**

The following substances are combined to form an emulsion. The percentages refer to percentages w/v of the final emulsion.

**Group A**

sorbitan tristearate or PolawaxNF 2.0%

	28
glycerol monostearate	2.0%
light liquid paraffin	10.0%
white soft paraffin	5.0%
isopropyl myristate	3.0%
5 benzyl alcohol	0.2%

Group B

	sodium cromoglycate	7.5%
	disodium edetate	0.1%
10	amphoteric surfactant	2.0%(for example disodium
	coacamphodiacetate, which may be compounded with lauryl sulphate and	
	hexylene glycol, for example Miracare 2MCA/E™)	
	alkoxylated cetyl alcohol	1.0%
	triclosan	0.2%
15	purified water	67.0%

The emulsion is prepared by heating the oils (compounds in group A) to about 70 °C, then adding them steadily to the water phase (compounds in Group B; also at or about 70 °C) with good stirring, and then allowing the

20 emulsion to cool. The batch size may be between about 10 litres and about 500 litres or more. The emulsion is prepared using a high shear homogeniser, as known to those skilled in the art. The mixture is stirred as the ingredients are mixed and stirring should continue until the mixture cools to room temperature. Overstirring of the mixture does not appear to

25 be detrimental. If the mixture is not stirred sufficiently, the emulsion may not form, or if it does form, may be unstable and may crack ie return to the component oil and water phases.

**Example 2: clinical trial of efficacy of the emulsion comprising sodium cromoglycate in the treatment of atopic dermatitis**

Patients for the clinical trial may be selected on the basis of a diagnosis of atopic dermatitis, or on the basis of a diagnosis of atopic dermatitis with total Serum IgE greater than 200 units/ml.

Patients may be of any age and may be children, for example aged 6 months to 5 years. Patients may have any level of severity of diagnosed atopic dermatitis, or may be selected on the basis of severity, for example those with mild or moderate disease only, those with active disease only (ie not disease in remission), those with severe disease only.

A suitable trial population may, for example, be children aged between 6 months and 5 years with total Serum IgE greater than 200 units/ml.

The clinical trial methodology will follow that recommended by the European Task Force on Atopic Dermatitis (29).

**Example 3: Effect of a composition of the invention on severity of skin symptoms caused by atopic dermatitis.**

The composition of the invention had the following composition:

Polawax NF 2.0%  
glycerol monostearate BP 2.0%  
light liquid paraffin BP 10.0%  
white soft paraffin BP 5.0%  
isopropyl myristate BPC 3.0%  
sodium cromoglycate 4.0%

- disodium edetate BP 0.1%  
Miranol 2.0%  
Procetyl AWS 1.0%  
triclosan 0.2%  
5 benzyl alcohol BP 0.2%  
Deionised water 70.5 %

The pH is adjusted to 6.0 using sodium dihydrogen orthophosphate.

10 **Background information**

Patient TR aged 3.5 years has suffered from severe atopic dermatitis since he was 3-5 weeks old. Treatment before using the composition of the invention was topical steroid applied two times per day. This had been applied for 3 years and was not effective.

15

**Treatment with the composition of the invention**

The patient began by applying Aureocort™ (triamcinolone acetonide [a potent corticosteroid] and chlortetracycline hydrochloride) and then the composition of the invention on top.

20

- After 3 days Aureocort™ was replaced with a milder steroid (Eumovate™, clobetasone butyrate [a moderately potent corticosteroid]) and the symptoms continued to improve. On day 13 the order was changed so The composition of the invention was applied first and then Eumovate™,  
25 but this was not found to be as effective and the skin became red and sore. On day 19 the application order was returned to Eumovate™ followed by the composition of the invention.



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On day 25 the patient became ill with a cold that exacerbated his skin symptoms and on day 26 stopped using the composition of the invention for three days as it was causing a feeling of heat. Aureocort™ was used on its own for 2 days and then with the composition of the invention for a further 6 days until the skin was almost clear, when the use of Eumovate™ followed by the composition of the invention was recommenced.

Another cold on day 35 affected the patient's asthma but did not worsen the eczema or stop the patient using the composition of the invention.

8 weeks after the start of treatment the skin was almost clear and there were hardly any sores or scabs on the patient's body.

#### Recording of results

The condition of the skin, itching and sleep lost due to itching were recorded every day and measured on a scale of 0 to 3 where 3=severe, 2=moderate, 1=slight and 0=none.

#### Results

The results of the treatment have been plotted in the graph shown in Figure 1. It shows the mean score per week for each symptom.

The symptoms improved immediately and after 3 days, the patient could be moved on to a milder topical corticosteroid treatment. In week 2, the deterioration may be due to applying the corticosteroid treatment after the composition of the invention. This may have been further exacerbated in week 3 by a cold. In weeks 4 and 5 the condition was brought under control by a combination of the composition of the invention and a

stronger corticosteroid and in week 6 the patient returned to the milder corticosteroid in combination with the composition of the invention.

5 The symptoms continued to improve and the patient's skin became almost clear and very smooth, such that by week 7 there were hardly any sores or scabs on the patient's body.

Further measurements were made of the area affected, the corticosteroid cream usage and the mother's assessment of the patient's condition. The  
10 first two showed a significant reduction, and the mother considered there to be a "fabulous improvement".

Seven other named patients between the ages of 3 and 25 were treated with the composition of the invention. Initially, some patients were given  
15 a 7.5% foam-based formulation. This proved effective. A burning sensation was noted by some patients, especially on areas of broken skin. Later, patients were given a 4% solution presented as a formulation of the invention, in particular the formulation described above. This has improved the skin condition in all patients. A burning sensation was  
20 noticed in some cases. Patients successfully controlled using the composition of the invention are able to reduce or eliminate steroid use, and 5 out of 7 patients are continuing to use the composition of the invention on a routine basis.

**Example 4: Tolerability and absorption studies.**

The studies are to assess the safety and tolerability of the composition of the invention described in Example 3, and to measure the systemic  
5 absorption of sodium cromoglycate. The formulations tested are those with 0%, 2%, 4% or 8% sodium cromoglycate.

The studies are double-blind, randomised, placebo-controlled, ascending dose studies.

10

Each subject receives only one of the above medication strengths which is applied topically twice daily for seven days to a pre-defined area on the forearms and abdomen. Thirty-six healthy volunteers are examined, at least four of which must be male and at least four of which must be  
15 female.

The subjects are dosed in three groups of 12 subjects each (nine to receive formulations comprising sodium cromoglycate and three to receive the formulation with no sodium cromoglycate). Seven days of treatment may  
20 be sufficient to reach steady state with this formulation.

The study formulation is administered by spreading evenly over the following areas: the volar aspects of both forearms and the abdomen. The study formulation is spread by the subject using two fingers of each hand.  
25 Sufficient formulation is used to just cover the defined area. The subject does not wear gloves. The container of study formulation for each subject is weighed before dosing. The site where the formulation is administered is left uncovered for one hour and is then covered up. The container is reweighed following dosing in order to determine the mass of study

formulation remaining. The dosing procedure is repeated at 12 hour intervals. The drug is applied to the same three areas of skin on each occasion for seven days (a total of 14 doses administered).

- 5 The drug administration sites are assessed before and after application for Draize scale assessments and skin symptoms, including itch.

Urine is collected for assay of the 24 hours cumulative urinary excretion of unchanged cromoglycate ( $A_{e_{0-24}}$ ) on the seventh day of drug treatment.

- 10 Although systemic absorption is best assessed in terms of plasma or serum drug concentrations, a sensitive assay for measurement of the anticipated low drug levels of sodium cromoglycate is not generally available. Urinary recovery is therefore used as a means of assessing drug absorption.

15

Urine samples are assayed for unchanged cromoglycate by liquid chromatography/mass spectrometry (LC/MS). The limit of quantification is 0.05 mg/L.

- 20 Assessment of adverse events, skin related symptoms and Draize scale assessments are measured. Subjects are questioned regarding itch and other skin-related symptoms.

- 25 It is expected that the formulation is found to be well-tolerated and that absorption is below the level seen with inhaled sodium cromoglycate. Sodium cromoglycate has a reputation for being a very safe drug in clinical practice and is well documented. However, some adverse effects do occur. These are generally reported as transient, the main ones being

headache, dizziness, local irritation of the target organ and an unpleasant taste in the mouth.

There are also some other effects that are dependent on the route of administration. Eye drops occasionally cause burning and stinging. Oral administration may cause nausea, skin rash and joint pain. Intra-nasal administration may cause epistaxis. For a topical formulation applied to the skin, irritation of the skin may cause a burning or stinging sensation.

10 Currently, the largest doses of sodium cromoglycate administered in clinical use are for asthma (20mg inhaled up to 8 times daily; maximum administered dose of 160mg, with 13-24 mg absorbed, given the bioavailability of 8-15%) and food allergy (up to 40 mg/kg/day orally; maximum administered dose of 2800 mg in a 70 kg man, with 28 mg  
15 absorbed given a bioavailability of 1%). The maximum dose for the present formulation is expected to be about 5 ml twice daily of an 8% sodium cromoglycate formulation. Thus the maximum administered topical daily dose is expected to be 800 mg. Topical bioavailability figures quoted in the literature are from 0.01 to 2.75%. This would mean that the  
20 maximum absorbed daily dose is expected to be 0.08 to 22 mg. The systemic dose is therefore expected to be below that achieved by other routes of administration.

Absorption of sodium cromoglycate through the skin may be measured by  
25 measuring the presence of sodium cromoglycate in plasma or urine following topical application as described above or as described, for example, in Ishikura *et al* (1987) cited above or in Ariyanayagam *et al* (20), as mentioned above.

**Example 5: Phase II clinical trials**

Trial 1: a single centre double-blind placebo controlled randomised  
5 crossover study using a 4% composition of the invention as described in  
Example 3 as an adjunct to steroid treatment in children aged 1 to 7 years  
with atopic dermatitis. Treatment time will be 12 weeks following a 4-  
week run-in. Evaluation criteria will include any reduction in topical  
corticosteroid use, SCORAD assessment scores, acceptability of treatment  
10 and adverse events.

Subjects are determined to have atopic dermatitis by reference to the  
diagnostic criteria of Hanifin and Rajika (Hanifin (1982) "Atopic  
dermatitis" *J Am Acad Dermatol* 6, 1-13). The atopic dermatitis is of  
15 moderate to severe grade according to the grading system of Rajika and  
Langeland (Rajika & Langeland (1989) "Grading of the severity of atopic  
dermatitis" *Acta Derm Venerol* 144(suppl) 13-14). On entry to the  
double-blind (treatment) phase, the subjects have a SCORAD score of 25  
or more.

20

The steroid treatment is with Betnovate RD™ (betamethasone valerate; a  
potent corticosteroid). This replaces any corticosteroid treatment  
previously used by the subject.

25 Diary cards are completed (by a parent) during the run-in and treatment  
phases. A urine sample is taken at the end of 12 weeks of test treatment  
in order to determine the absorption of sodium cromoglycate, as described  
in Example 4. The severity of itching and sleep disturbance due to atopic

dermatitis are recorded twice daily. Global assessments of effectiveness and acceptability of the treatment are also made by the parent.

The order of application of the test lotion and the topical corticosteroid may be specified: for example, the topical corticosteroid may be applied at least 15 minutes after applying the test lotion. The lotion is applied to the affected area of the skin twice daily.

Trial 2: a single centre double-blind placebo controlled randomised crossover study to evaluate the acceptability, tolerability and effects of 3 days pretreatment with 2%, 4% and 8% compositions of the invention on the size of the skin wheal and flare response and itch caused by antigen challenge in volunteer allergic adults.

Kimata and Igarashi (1990) *Allergy* 453, 393-395 and Phillips *et al* (1996) *Allergy* 51(3), 198-199 have shown that topical sodium cromoglycate inhibits antigen induced wheal and flare reaction in the skin of human subjects. The results of the latter study indicated that a significant effect is observed only after pretreatment (in this case for 3 days) and not after a single dose immediately preceding skin prick testing.

Sodium cromoglycate may have an effect on antigen mediated reactions in the skin of humans and that these effects are relevant to its potential clinical efficacy in conditions such as atopic dermatitis. Any clinical effect is likely to be dependent upon the formulation used achieving good penetration of the skin in order to get to the relevant cells and receptors in the dermis. The demonstration of an inhibitory effect together with a reduction in the associated itching on use of a particular formulation may be supportive of the use of the formulation in paediatric atopic dermatitis

and may also provide useful data for the selection of the optimum concentration.

- 5 Subjects have a positive skin challenge test response to at least two common allergens, greater than or equal to that of the positive control and at least equal to 10 mm<sup>2</sup>. Allergens are selected from the following: grass, ragweed tree pollen, cat fur or house dust mite. Subjects undergo skin prick tests with antigens diluted to give mild to moderate wheal responses  
10 of 3-5 mm in diameter. Subjects are then allocated to receive in random order each of four treatments (2%, 4%, 8% sodium cromoglycate or placebo), to be applied four times a day for 3 days to one forearm. On day 4, following a final treatment application, subjects are re-challenged with antigen, and the areas of wheal and flare responses and level of  
15 itching are assessed after 15 minutes. Treatment periods are separated by washout periods of at least 4 days. Criteria for evaluation are the size of wheal and flare responses to allergen 15 minutes post challenge and the degree of itching at this time as assessed by the VAS scale.

20 **Example 6: Phase III clinical studies**

Two studies are performed as follows:

- 1)  
25 250 patients with moderate to severe atopy.  
Run-in on topical corticosteroid therapy for one month.  
Randomised to placebo or active treatment for three months.  
Disease modification, measured using standard parameters, and reduction in the amount of corticosteroid used are used to assess treatment efficacy.



A long-term open follow-up is carried out.

2)

5 250 patients with mild atopy.

Run-in on intermittent topical corticosteroid therapy for one month.

Randomised to placebo or active treatment for three months.

Disease modification, measured using standard parameters, is used to assess treatment efficacy.

10

A long-term open follow-up is carried out.

Results follow those seen in named patients, as summarised in Example 3.

An improvement in symptoms is seen, accompanied by reduced need for  
15 corticosteroid treatment. The treatment is well tolerated.

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CLAIMS

1. A composition comprising an amphoteric surfactant, an alkoxy-  
5 cetyl alcohol and a polar drug.
2. A composition according to claim 1 wherein the drug is an anionic  
drug.
- 10 3. A composition according to claim 1 or claim 2 wherein the amphoteric  
surfactant is a balanced amphoteric surfactant.
4. A composition according to any of the preceding claims wherein the  
alkoxy- cetyl alcohol is Procetyl AWS.
- 15 5. A composition according to any of the preceding claims wherein the  
amphoteric surfactant comprises disodium coacoamphodiacetate.
6. A composition according to any of the preceding claims wherein the  
20 drug comprises sodium cromoglycate or nedocromil sodium.
7. A composition according to any one of claims 1 to 5 wherein the drug  
comprises a corticosteroid or an antibacterial agent.
- 25 8. A composition according to any one of claims 1 to 5 wherein the drug  
comprises an antirheumatic agent, nicotine or a hormone.
9. A composition according to claim 6 wherein the composition further  
comprises a corticosteroid.

10. A composition according to any one of the preceding claims wherein the composition comprises an aqueous phase and an oil phase.

5 11. A composition according to claim 10 wherein the composition is an oil-in-water emulsion.

12. A composition according to any one of the preceding claims wherein the composition is a foam.

10

13. A composition according to any of the preceding claims consisting substantially of:

sorbitan tristearate or non-ionic emulsifying wax 0.5 to 5%w/v

glycerol monostearate 0.5 to 5%w/v

15 light liquid paraffin 1 to 20% w/v

white soft paraffin 1 to 10%w/v

iso propyl myristate 0.5 to 5% w/v

drug 0.1 to 20% w/v

disodium edetate 0.01 to 1% w/v

20 amphoteric surfactant 0.1 to 10% w/v

alkoxylated cetyl alcohol 0.1 to 10% w/v

triclosan 0.01 to 1% w/v

benzyl alcohol 0.01 to 1% w/v

purified water to 100% v/v of the emulsion

25

14. A stable oil-in-water emulsion comprising sodium cromoglycate, wherein when the emulsion is applied to skin an amount of sodium cromoglycate penetrates the skin that is sufficient to produce a demonstrable effect in the treatment of atopic dermatitis/eczema.

15. A method of treatment of a skin disease or condition wherein a drug is applied to the skin of an individual affected by the disease or condition in or with a formulation comprising alkoxylated cetyl alcohol and an amphoteric surfactant.

16. Use of an alkoxylated cetyl alcohol and an amphoteric surfactant in the manufacture of a medicament for the treatment of a skin disease or condition.

17. A method of treatment of a skin disease or condition comprising applying a composition or emulsion according to any one of claims 1 to 14 to the skin of an individual affected by the disease or condition.

18. Use of a composition or emulsion according to any one of claims 1 to 14 in a method of treating a skin disease or condition.

19. Use of a composition or emulsion according to any one of claims 1 to 14 in the manufacture of a medicament for the treatment of a skin disease or condition.

20. Use according to claim 18 or 19 wherein the disease or condition is one in which skin mast cells and/or delayed (cellular) hypersensitivity reactions and/or inflammation is thought to be involved.

21. Use according to any one of claims 18 to 20 in which the disease or condition is atopic dermatitis or eczema, contact sensitivity, psoriasis, drug sensitivity reactions, aphthous ulcers, Behçet's syndrome, pemphigus, urticaria, urticaria pigmentosa, pyoderma gangrenosum, chronic skin

ulcers, ulcers associated with Crohn's disease, burns, insect stings/bites, herpetic infections, systemic sclerosis (systemic scleroderma), morphoea (circumscribed or localised scleroderma), dermal nodular fibrosis or sunburn.

5

22. The use according to claim 16, 18 to 21 or method according to claim 15 or 17 wherein the skin disease or condition is, has been or will be further treated by application of a corticosteroid.

10

23. A method of treatment of a patient in need of a polar drug comprising applying a composition or emulsion according to any one of claims 1 to 13 comprising the said polar drug to the skin of the said patient.

15

24. The use of a composition or emulsion according to any one of claims 1 to 13 in a method of treating a patient in need of the said polar drug.

20

25. The method of claim 23 or use of claim 24 wherein the said patient is a patient with arthritis and wherein the said polar drug is a polar anti-inflammatory or antirheumatic agent.

25

26. The method of claim 23 or use of claim 24 wherein the said patient is a patient with acne and wherein the said polar drug is a polar antibacterial drug.

27. The method of claim 23 or use of claim 24 wherein the said patient is a patient in need of nicotine and wherein the said polar drug is nicotine.

28. The composition or emulsion of any one of claims 1 to 14 packaged in a tube, tub, bottle or pressurised aerosol container.



29. A composition or emulsion according to any one of claims 1 to 14 for use in medicine.

**AMENDED CLAIMS**

[received by the International Bureau on 25 October 1999 (25.10.99);  
new claim 30 added; remaining claims unchanged (1 page)]

- 5 30. A composition, method or use according to any of claims 1 to 13 or  
15 to 29 (when dependent on claims 1 to 13), wherein the alkoxylated  
cetyl alcohol is polypropoxylated cetyl alcohol.

Effect of an emulsion comprising sodium cromoglycate on severity of skin symptoms caused by atopic dermatitis

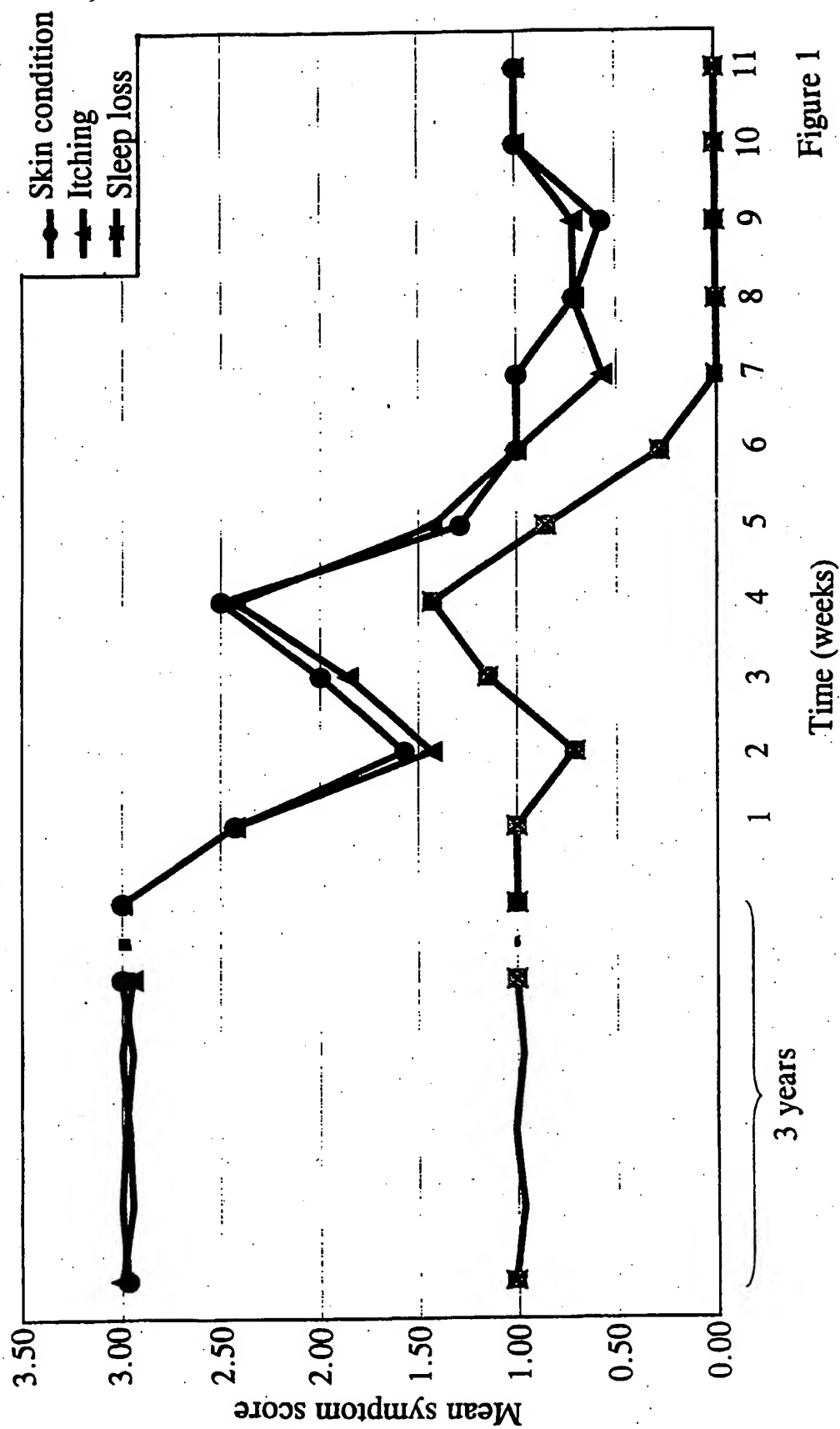


Figure 1

# INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 99/01600

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 A61K9/107 A61K9/12 A61K31/35

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>ARIYANAYAGAM M. ET AL.: "Topical sodium cromoglycate in the management of atopic eczema-a controlled trial"</p> <p>BR.J.DERMATOL.,</p> <p>vol. 112, no. 3, March 1985 (1985-03),</p> <p>pages 343-348, XP002113842</p> <p>u.k.</p> <p>cited in the application</p> <p>abstract</p> <p>page 343, paragraph 4 - paragraph 5</p> <p>page 344, paragraph 2</p> <p>page 344, last paragraph</p> <p>page 345, paragraph 2</p> <p>page 347, paragraph 3 - page 348,</p> <p>paragraph 2</p> <p style="text-align: center;">---</p> <p style="text-align: center;">-/--</p>	<p>14,</p> <p>17-21,29</p>

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

### \* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
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Date of the actual completion of the international search

31 August 1999

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